Fampridine-induced changes in walking kinetics are associated with clinical improvements in patients with multiple sclerosis

Weller, D ; Lörincz, L ; Sutter, T ; Reuter, K ; Linnebank, M ; Weller, M ; Zörner, B ; Filli, L

Abstract: Gait dysfunction is common in patients with multiple sclerosis (PwMS). Treatment with prolonged-release fampridine (PR-fampridine) improves walking ability in some PwMS. Associated fampridine-induced changes in the walking pattern are still poorly understood but may provide a better understanding of the mechanisms underlying the beneficial drug effects. 61 PwMS were treated with PR-fampridine in a randomized, monocentric, double-blind and placebo-controlled clinical trial with crossover design (FAMPKIN). Drug-induced improvements in walking speed (Timed-25-Foot Walk; T25FW) and endurance (6-Minute Walk Test; 6MWT) were quantified. In this sub-study of the FAMPKIN trial, fampridine-induced changes in kinetic gait patterns were analyzed by pressure-based foot print analysis during treadmill walking. Vertical ground reaction forces were analyzed during different gait phases. Kinetic data of 44 PwMS was eligible for analysis. During double-blind treatment with PR-fampridine, patients performed significantly better in the T25FW and 6MWT than during placebo treatment ($p < 0.0001$ for both). At the group level ($n = 44$), there were no significant changes of gait kinetics under PR-fampridine vs. placebo. However, we found relevant changes of walking kinetics regarding forces during loading, single limb and pre-swing phase in a patient sub-group ($n = 8$). Interestingly, this sub-group demonstrated superior responsiveness to PR-fampridine in the clinical walking tests compared to those patients without any fampridine-induced changes in kinetics ($n = 36$). Our results demonstrate fampridine-induced changes in gait kinetics in a sub-group of PwMS. These gait pattern changes were accompanied by improved clinical walking performance under PR-fampridine. These results shed some light on the biomechanical changes in walking patterns underlying enhanced fampridine-induced gait performance.

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Abstract

Gait dysfunction is common in patients with multiple sclerosis (PwMS). Treatment with prolonged-release fampridine (PR-fampridine) improves walking ability in some PwMS. Associated fampridine-induced changes in the walking pattern are still poorly understood but may provide a better understanding of the mechanisms underlying the beneficial drug effects. 61 PwMS were treated with PR-fampridine in a randomized, monocentric, double-blind and placebo-controlled clinical trial with crossover design (FAMPKIN). Drug-induced improvements in walking speed (Timed-25-Foot Walk; T25FW) and endurance (6-Minute Walk Test; 6MWT) were quantified. In this sub-study of the FAMPKIN trial, fampridine-induced changes in kinetic gait patterns were analyzed by pressure-based foot print analysis during treadmill walking. Vertical ground reaction forces were analyzed during different gait phases. Kinetic data of 44 PwMS was eligible for analysis. During double-blind treatment with PR-fampridine, patients performed significantly better in the T25FW and 6MWT than during placebo treatment ($p<0.0001$ for both). At the group level (n=44), there were no significant changes of gait kinetics under PR-fampridine vs. placebo. However, we found relevant changes of walking kinetics regarding forces during loading, single limb and pre-swing phase in a patient sub-group (n=8). Interestingly, this sub-group demonstrated superior responsiveness to PR-fampridine in the clinical walking tests compared to those patients without any fampridine-induced changes in kinetics (n=36).

Our results demonstrate fampridine-induced changes in gait kinetics in a sub-group of PwMS. These gait pattern changes were accompanied by improved clinical walking performance under PR-fampridine. These results shed some light on the biomechanical changes in walking patterns underlying enhanced fampridine-induced gait performance.

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) and the primary cause of persisting motor disability including impaired walking function and mobility in young adults.[1]

Treatment with prolonged-release (PR) fampridine (4-aminopyridine, dalfampridine) improves MS-associated gait disorders.[2,3] 4-aminopyridine is a potassium channel blocker enhancing signal conduction in demyelinated nerve fibers.[4] Treatment with prolonged-release (PR) fampridine results in enhanced walking speed, endurance as well as improved balance and self-perceived walking function.[5-11] Whereas the effects of PR-fampridine on clinical walking performance are well investigated, only little information exists on drug-induced modifications of the gait pattern that might underlie the improvement in walking capacity.

Instrumented gait analysis based on kinematic (i.e. quantification of movements) or kinetic (i.e. quantification of forces during motion) techniques enables an objective and comprehensive quantification of walking quality. To date, the effects of PR-fampridine on MS-related pathologies of the gait pattern are poorly understood.[3] Previous data demonstrated fampridine-induced changes of gait kinematics: these changes were heterogeneous across patients, but correlated with improvements in clinical walking tests.[11] In contrast to cost- and time-intensive full body kinematics, kinetic gait analysis is an easily applicable, fast, and widely used technique in research and clinical settings that has demonstrated high sensitivity in describing MS-associated walking impairments.[12-15]

This study aimed at characterizing fampridine-induced changes in gait patterns of PwMS using pressure-based kinetic foot print analysis. In a second step, the study investigated the influence of drug-induced changes in gait kinetics on patients' clinical walking performance (i.e. gait speed, endurance), thus trying to shed some light onto the locomotor mechanisms that might underlie the beneficial effects of PR-fampridine on gait function in PwMS.

Methods

Study participants

This study (FAMPKIN; clinicaltrials.gov; NCT01576354) was performed at the University Hospital Zurich. Sixty-one subjects with MS defined by the McDonald criteria (disease duration > 3 months)[16] with a clinically apparent walking impairment were analyzed. Patients unable to walk a distance of at least 50 meters within a period of 6 minutes (with or without assistive devices) were excluded. Further inclusion and exclusion criteria are described elsewhere.[11] All participants gave written informed consent. The study was approved by the Zurich cantonal ethics committee. All experimental procedures were performed according to the Declaration of Helsinki and the Good Clinical Practice guidelines. The present manuscript describes results of a sub-study (gait kinetics) performed within the framework of the FAMPKIN trial.

Study design

This monocentric, phase II study was conducted as randomized, placebo-controlled, double-blind trial with crossover design (Figure 1A).[11] An initial screening visit was followed by a 2-week run-in phase with single-blind placebo treatment. Afterwards, patients were randomized into two groups, one of which was treated with PR-fampridine (Biogen, Cambridge, MA) first (for 6 weeks), the other received placebo (Biogen, Cambridge, MA) in a double-blind fashion. Treatment was changed after a two-week wash-out period (i.e. single-blind placebo treatment) between visit 6 and 7. PR-fampridine and placebo tablets were taken orally twice daily (12h apart). Patients did not receive any study medication for the last two weeks of the trial (follow-up). All experimenters and patients were blinded to the treatment allocation at the time of assessment. Blinding and randomization was conducted by the Zurich cantonal pharmacy.

Outcome measures

Maximal walking speed (timed 25-foot walk; T25FW)[17] and walking endurance (6-minute walking test; 6MWT)[18] were used as core clinical outcome measures[19] and were assessed at

all double-blind visits (V3-6 and V8-11).[11] Assistive walking devices were used as required during clinical walking tests. The usage of particular walking aids (i.e. walking sticks, crutches, walking frames) were kept identical for all walking tests of a given individual during the trial. Treadmill-based kinetic gait analysis was performed at two visits during each treatment phase (V4/V6, V9/V11). If required, subjects were allowed to hold on the handrails during walking. An instrumented treadmill with integrated pressure plate (FDMTHM-M-2i System, zebris Medical GmbH, Germany) was used to measure vertical ground reaction forces during walking.[11] Walking conditions (i.e. walking speed, use of handrails etc.) were kept constant across all visits of the trial, thus enabling a precise comparison of drug effects on ambulatory function. Prior to kinetic analysis, all patients were familiarized with treadmill walking to assure a stable walking pattern.[20] Walking speed for each patient was fixed at half-maximal gait velocity (v50%) as determined by the T25FW, thus adjusting gait speed to the individual impairment level (regarding walking speed).[11,21,22] Patients were analyzed while walking barefoot for >30 seconds on the treadmill.

Data analysis

Results of the T25FW, 6MWT and kinetic gait analysis were assessed during the double-blind treatment phases with PR-fampridine and placebo and were expressed as change under PR-fampridine compared to placebo performance.

Kinetic parameters were assessed per gait cycle which was defined as time interval between two consecutive heel strikes of the same leg. The stance phase was divided into three sub-phases being defined as initial loading phase, single stance phase and pre-swing (i.e. push off) phase. Loading phase was defined between the initial contact of the ipsilateral foot and toe off of the contralateral foot. This phase corresponds to the pre-swing phase of the contralateral foot (i.e. interval between the initial contact of the contralateral foot and the last contact of the ipsilateral foot). Single stance phase was defined as period during which only one foot contacts the floor.

Kinetic data during the different gait phases were expressed as averaged values and as summated value over the respective phases. Summated values were used to obtain information concerning the cumulative force applied during the particular gait phase. The more impaired leg of each patient was determined by neurological examination as described previously.[11] To avoid confounding effects of changing body weight on kinetic analysis, pressure data of each patient was normalized to his respective body weight at each single visit. This normalization allowed for comparisons of kinetic data between different visits and patients.

To further assess the impact of fampridine-induced changes in gait kinetics on improvements in clinical walking function (i.e. the T25FW, 6MWT), participants were divided into two sub-groups, one of which containing patients without any fampridine-induced changes in gait kinetics (no kinetic adaptations, NKA group). The second sub-group (kinetic adaptations; KA group) consisted of patients revealing at least one relevant change in any kinetic parameter (see definition below) under PR-fampridine relative to placebo treatment (Figure 1B).

Statistical analysis

Statistical analysis was performed by SPSS (V23, SPSS Inc., CA, USA) and Matlab (Mathworks, Inc., USA).

Demographic differences between the two sub-groups (i.e. NKA vs. KA group: Table 1) were assessed by unpaired, two-tailed t-test (age, disease duration), Mann-Whitney test (expanded disability status scale (EDSS) score), Fisher's Exact test (gender) and Pearson Chi-Square test (MS type). Differences in kinetic gait parameters and clinical gait tests between the double-blind treatment phases were analyzed by paired, two-tailed t-tests. Statistical comparisons were followed by Bonferroni post-hoc correction for multiple testing. Unpaired, two-tailed t-tests were used to analyze differences in the performances of different patient subgroups. Relevant changes in kinetic parameters for single subjects were evaluated by calculating the between-measurement variability (measurement error) within each double-blind treatment period for each kinetic parameter. Relevant, drug-induced changes were

defined as changes that exceeded or undershot the between-measurement variability by 2 standard deviations when comparing treatment phases.[11]

Results

Of 61 patients, 44 participants were eligible for kinetic gait analysis. Whereas six patients were not included in the data analysis of the FAMPKIN trial,[11] eleven participants were excluded from kinetic analysis (4 patients did not consistently walk within the pressure-sensitive area of the treadmill; 1 patient changed its walking assistance (handrails) between measurements; 6 patients were excluded due to impaired foot clearance). The study population (n=44) was 49.8 (± 9.6) years of age, consisted of 27 females (61%) and revealed a mean disease duration of 12.4 (± 8.3) years (Table 1). Patients (21 relapsing-remitting, 4 primary-progressive and 19 secondary-progressive MS) showed a mean disability of 4.6 ± 1.3 points in the expanded disability status scale (EDSS). Most PwMS walked unassisted on the treadmill (n=35), some patients were holding on to the handrails unilaterally (n=3) or bilaterally (n=6). Average treadmill walking speed was 0.61 ± 0.22 m/s.

As for the total study population,[11] maximal walking speed (T25FW) and endurance (6MWT) were significantly improved under PR-fampridine compared to placebo in the sub-population of patients undergoing kinetic assessment (n=44; $p<0.0001$ for T25FW and 6MWT; paired, two-tailed t-test).

There were no overall drug-induced changes in any assessed kinetic parameter at the level of the total population (n=44) for the less- (LI) and more-impaired (MI) leg (Table 2). However, multiple changes in kinetic walking parameters as induced by PR-fampridine were observed at the single patient level. Patients revealing at least one relevant change in any kinetic parameter under PR-fampridine relative to placebo treatment (Figure 1B; see methods for definition of relevant change) were assigned to the kinetic adaptations (KA) group (n=8). Patients within this group showed heterogeneous changes in gait patterns: single limb support (mainly of the more-impaired leg) was enhanced by PR-fampridine in 4 patients, whereas pre-

swing phase during terminal stance phase was increased in 3 patients (Figure 1B). The majority of kinetic changes under PR-fampridine (13 of 18) resulted in enhanced ground reaction forces in patients' more-impaired leg.

Demographic data were not different between the NKA and KA subgroups (Table 1). Responders showed an enhanced disability status (EDSS: responders vs. non-responders: 5.6 ± 1.1 vs. 4.4 ± 1.2; $p = 0.0135$; unpaired, two-tailed t-test) and a higher proportion of secondary progressive MS (MS types: responders vs. non-responders: $p = 0.013$; Pearson Chi-Square: 0.019). Both differences, however, were not significant after Bonferroni post-hoc correction for multiple testing.

In a next step, we compared drug-induced effects on gait kinetics and clinical walking function in patients with (KA group; n=8) and without drug-induced kinetic adaptations (NKA group; n=36). Patients in the KA group revealed higher drug-induced improvements in maximal walking speed (T25FW) and walking endurance (6MWT) than patients without fampridine-induced changes in walking kinetics (i.e. NKA group; T25FW: $p=0.0135$; 6MWT: $p=0.0296$; unpaired, two-tailed t-test; Figure 1C, D).

Discussion

The present study demonstrated significant improvements in maximal walking speed (T25FW) and endurance (6MWT) upon double-blind treatment with PR-fampridine vs. placebo in the investigated sub-population of the FAMPKIN trial, thus confirming previous reports on the effects of PR-fampridine in gait-impaired PwMS.[5,7,8,10,11] The primary aim of this study was to assess drug-induced changes in gait kinetics and to elucidate whether these locomotor adaptations might be a potential mechanisms underlying the well-documented positive drug-effects on clinical walking performance. Mean kinetic parameters did not reveal drug-induced changes over the total population. On the single subject level, however, a subset of patients (8 of 44) revealed considerable drug-induced changes in gait kinematics. These kinetic changes were different across patients, possibly reflecting the heterogeneous nature of MS-related symptoms that lead to gait impairments (e.g. spasticity, paresis, ataxia, sensory impairments etc.).[21,23] This finding agrees with previous studies reporting that fampridine-induced changes of different gait parameters rarely show group mean effects, as drug-induced gait adaptations are heterogenous across patients.[5,11] The specific changes in kinetic parameters as induced by PR-fampridine might therefore depend on the individual impairment profile of each patient. The majority of patients demonstrating PR-fampridine induced changes in kinetic gait patterns (i.e. KA group) were diagnosed with secondary progressing MS and revealed higher EDSS scores compared to non-responding patients. This is in line with previous findings reporting that PwMS with higher levels of functional disability show enhanced responsiveness to PR-fampridine compared to mildly impaired PwMS.[24-26] Superior positive drug responses in patients with severe MS-related impairments might be attributed to more pronounced axonal demyelination and neural damage in these patients. Given that fampridine enhances axonal conduction by blocking potassium channels along demyelinated axons,[27,28] patients with extensive demyelination (and higher disability) might benefit more from this treatment.

PR-fampridine resulted in enhanced ground reaction forces primarily concerning patients' more-impaired legs which might imply that changes in gait patterns are based on restoration of primary deficits instead of compensatory strategies. Three of eight patients within the KA group demonstrated enhanced vertical forces during the pre-swing phase under PR-fampridine which might be indicative for improved gastrocnemius muscle function leading to faster walking speed in fampridine-treated PwMS.[29] In multiple patients, we found significant increases in the produced forces during the single limb phases. Previous reports demonstrated that PwMS reveal prolonged periods of double limb support compared to healthy controls, probably to compensate for impaired dynamic stability during walking.[30-32] The significant increase of forces during single stance phase under PR-fampridine may indicate a shift from a pathological towards a more physiological gait pattern.[33-35]

One major finding of this sub-study is that patients in the KA group showed greater fampridine-induced improvements in the clinical walking tests compared to those patients that demonstrated no relevant changes in their gait kinetics. Thus, changes in gait kinetics may lead to improvements in walking performance as measured in clinical walking tests. This is in agreement with our earlier findings that fampridine-induced changes in 3D kinematic gait parameters correlated with enhanced walking performance in these patients.[11] Compared with 3D kinematic gait analysis, pressure-based gait analysis (e.g. GAITRite or instrumented treadmills) is less cost- and time-intense and widely used in clinics. The straightforward appliance of kinetic methodologies enables to investigate biomechanical changes as induced by PR-fampridine in larger patient cohorts, thus fostering the mechanistic understanding of how PR-fampridine enhances walking performance in gait-impaired PwMS.

A limitation of this study is that a small subset of PwMS required handrail support during walking, which potentially confounds kinetic gait assessments. However, walking conditions (i.e. gait speed, handrail support) was kept constant for each individual across all longitudinal measurements, thus enabling an accurate and precise comparison of gait parameters under PR-fampridine and placebo. Walking barefoot during kinetic gait assessments might has been disabling for some patients, however, it enabled an accurate characterization of the pure,

uncorrected walking pathology without compensation by external devices (e.g. shoes with orthopedic inlays, ankle braces). Due to the small sample size (particularly of subjects with kinetic adaptations), our findings need to be interpreted cautiously and require to be confirmed by future studies investigating the relation between qualitative and quantitative gait changes in response to PR-fampridine.

Conclusion

Our findings indicate that PR-fampridine leads to changes in gait kinetics in a subset of PwMS. Drug-induced adaptations in kinetics were associated with more pronounced improvements in clinical walking tests, suggesting that changes in the walking pattern may translate into improved gait function.

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Data availability statement

All data generated or analyzed during this study are included in this published article ~~[and its supplementary information files]~~.

Declaration of interest

DW reports no disclosures.

LL reports no disclosures.

TS reports no disclosures.

KR received travel grants from Biogen.

MW received funding from Biogen.

ML received honoraria, travel grants and funding from Biogen. He is a consultant to Biogen.

BZ received honoraria, travel grants and funding from Biogen.

LF reports no disclosures.

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Figure legend

Figure 1. (A) After the screening visit (S), patients were treated with placebo (single-blind, run-in) for two weeks. Two 6-week double-blind treatment phases with PR-fampridine and placebo were separated by a 2-week washout phase (single-blind placebo treatment) between visits 6 and 7. Patients first treated with PR-fampridine (grey treatment arm) were afterwards treated with placebo and vice versa (cross-over design). During the 2 weeks follow-up, patients received no study drugs. Total duration of the study was 18 weeks. **(B)** Individual changes in kinetic gait parameters under PR-fampridine relative to placebo treatment on the single subject level. Changes exceeding (light grey) or undershooting (dark grey) the averaged variability between measurements (measurement error) ± 2 standard deviations are highlighted. **(C)**/**(D)** Changes in gait kinetics are related to improvements in clinical walking tests. Patients with changes in at least one kinetic parameter under PR-fampridine (i.e. KA group, n=8) showed a better response (improvement) to PR-fampridine than patients in the NKA group (n=36) in clinical walking tests (C: T25FW, D: 6MWT). Statistical analysis was performed by unpaired, two-tailed t-tests. Asterisk indicates p-value < 0.05. Abbreviations: AVG: average value over the respective gait phase; KA group: kinetic adaptations group; NKA group: no kinetic adaptations group; LI: less impaired; MI: more-impaired. SUM: cumulative value over the respective gait phase.

Table 1. Demographic data of the study population. Data are shown for the total study population (n=44), for patients with fampridine-induced kinetic gait adaptations (KA group; n=8) and for patients without any changes in kinetic parameters (NKA; n=36). Abbreviations: EDSS: expanded disability status scale; KA; kinetic adaptations group; NKA; no kinetic adaptations group; PPMS: primary progressive multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

Table 2. Fampridine-induced changes in kinetics over the total study population (n=44). Abbreviations: AVG: average value over the respective gait phase; SUM: cumulative value over the respective gait phase; LI: less-impaired; MI: more-impaired.

Table 1

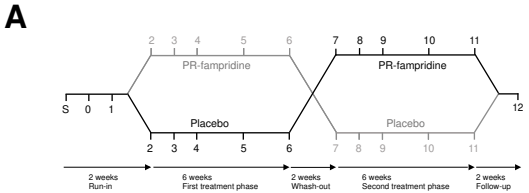
		Total cohort (n = 44)	**KA group** (n = 8)	**NKA group** (n = 36)
Age, y, mean ± SD		49.6 ± 9.9	50.4 ± 8.9	49.4 ± 10.3
Gender, number (%)	Male	17 (39)	3 (38)	14 (39)
	Female	27 (61)	5 (62)	22 (61)
EDSS score, mean ± SD (range)		4.6 ± 1.3 (2.5 – 6.5)	5.6 ± 1.1 (3.5 – 6.5)	4.4 ± 1.2 (2.5 – 6.5)
Type of MS, number (%)	RRMS	21 (48)	1 (13)	20 (56)
	PPMS	4 (9)	0	4 (11)
	SPMS	19 (43)	7 (87)	12 (33)
Disease duration, y from diagnosis, mean ± SD		12.4 ± 8.3	12.0 ± 8.5	12.5 ± 8.2

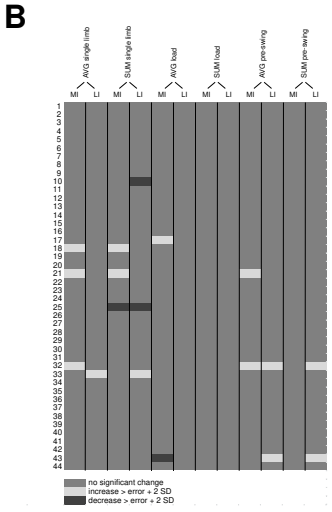
Table 1. Demographic data of the study population. Data are shown for the total study population (n=44), for kinetic responders (n=8) and for kinetic non-responders (n=36). Abbreviations: EDSS: expanded disability status scale; KA group: kinetic adaptations group; NKA group: no kinetic adaptations group; PPMS: primary progressive multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis.

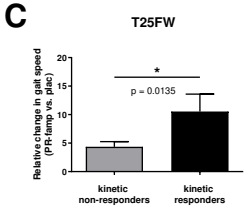
Table 2

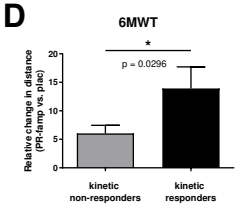
	MI leg		p-value	LI leg		p-value
	placebo mean [N/cm^2]	**fampridine mean** [N/cm^2]		**placebo mean** [N/cm^2]	**fampridine mean** [N/cm^2]	
single stance AVG	0.909	0.917	0.105	0.914	0.924	0.053
single stance SUM	35.587	35.651	0.905	37.437	37.531	0.891
load AVG	0.491	0.495	0.315	0.537	0.536	0.856
load SUM	14.213	14.507	0.317	16.212	16.07	0.597
pre-swing AVG	0.471	0.479	0.079	0.499	0.503	0.465
pre-swing SUM	13.854	14.192	0.214	14.844	14.784	0.768

Table 2. Fampridine-induced changes in kinetics over the total study population (n=44). Differences between kinetic parameters under PR-fampridine and placebo were compared by paired, two-tailed t-tests. Abbreviations: AVG: average value over the respective gait phase; SUM: cumulative value over the respective gait phase; LI: less-impaired; MI: more-impaired.


A
2 3 4 5 6 7 8 9 10 11
PR-fampridine
PR-fampridine
S 0 1
Placebo
Placebo
12
2 3 4 5 6 7 8 9 10 11
2 weeks
Run-in
6 weeks
First treatment phase
2 weeks
Whash-out
6 weeks
Second treatment phase
2 weeks
Follow-up


B
AVG single limb
SUM single limb
AVG load
SUM load
AVG per-swing
SUM per-swing
MI
LI
no significant change
increase > error + 2 SD
decrease > error + 2 SD


C
T25FW
Relative change in gait speed (PR-lamp vs. plac)
*
p = 0.0135
kinetic non-responders
kinetic responders


D
6MWT
Relative change in distance (PR-lamp vs. plac)
*
p = 0.0296
kinetic non-responders
kinetic responders